NASA SMART Probes
Cutting Edge Technology

Application to Breast Cancer Diagnosis

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NASA SMART Probe: Breast Cancer Application

Presenter: Robert W. Mah, Ph.D.

ABSTRACT

There is evidence in breast cancer and other malignancies that the physiologic environment within a tumor correlates with clinical outcome. We are developing a unique percutaneous Smart Probe to be used at the time of needle biopsy of the breast. The Smart Probe will simultaneously measure multiple physiologic parameters within a breast tumor. Direct and indirect measurements of tissue oxygen levels, blood flow, pH, and tissue fluid pressure will be analyzed in real-time. These parameters will be interpreted individually and collectively by innovative neural network techniques using advanced intelligent software.

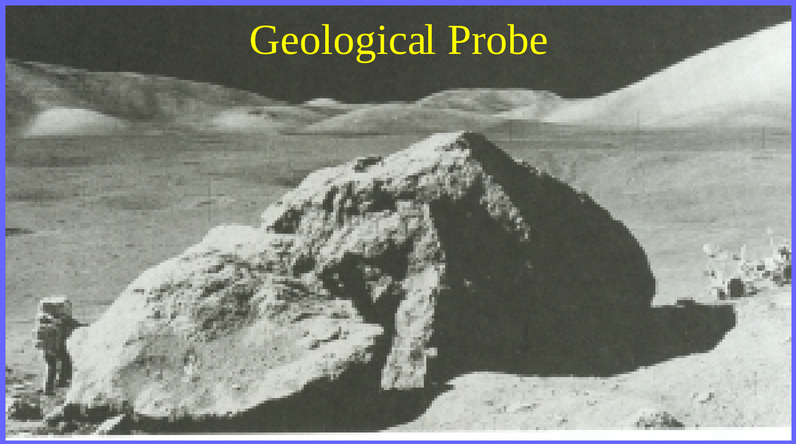
The goals are 1) develop a percutaneous Smart Probe with multiple sensor modalities and applying advanced Information Technologies to provide real-time diagnostic information of the tissue at tip of the probe, 2) test the percutaneous Smart Probe in women with benign and malignant breast masses who will be undergoing surgical biopsy, 3) correlate probe sensor data with benign and malignant status of breast masses, 4) determine whether the probe can detect physiologic differences within a breast tumor, at its margins, and in adjacent normal breast tissue, 5) correlate probe sensor data with known prognostic factors for breast cancer, including tumor size, tumor grade, axillary lymph node metastases, estrogen receptor and progesterone receptor status.

Use of the Smart Probe will be integrated into existing Stanford programs focusing on minimally invasive breast cancer diagnosis and treatment using 3-D breast ultrasound, breast MRI, percutaneous needle biopsy, and percutaneous radiofrequency ablation of breast cancer.

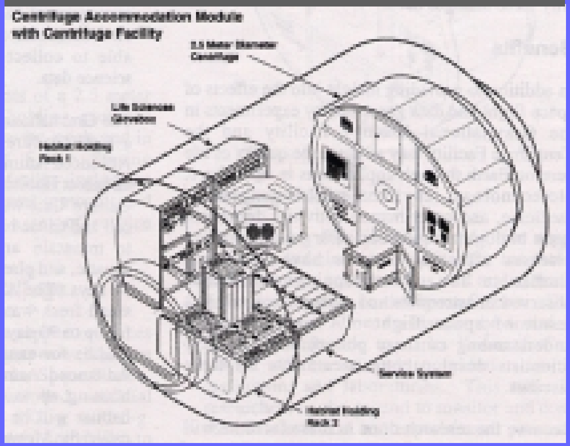
The long-term goal of this project is to develop a device (the NASA SMART Probe) for minimally invasive real-time identification and characterization of biological tissues. There are two basic concepts: (1) multiple microsensors measure different properties of the tissue under investigation in real-time; (2) "biologically-inspired" soft computing methodologies (hybrid neural networks and fuzzy logic) provide instantaneous synthesis of the high-dimensional data gathered by the multiple microsensors. The resulting unique "signature" for the tissue at the tip of the probe can then be compared with an increasingly rich databank of information gathered from other patients and normal individuals.

NASA SMART Probes

Geological Probe



Biomedical Research Probe



Medical Diagnosis Probe

Application of Advanced Information Technologies

To improve the safety, accuracy, and efficiency of critical procedures
To reduce the skill level to perform the procedure

Breast Cancer SMART Probe

- In vivo sensing of physiologic parameters o
- Real-time diagnosis of breast tissue at tip
- Enable accurate & efficient treatment
- Monitoring effects of treatment

Breast Surgeons Collaborating in the Development of a Breast Cancer SMART Probe

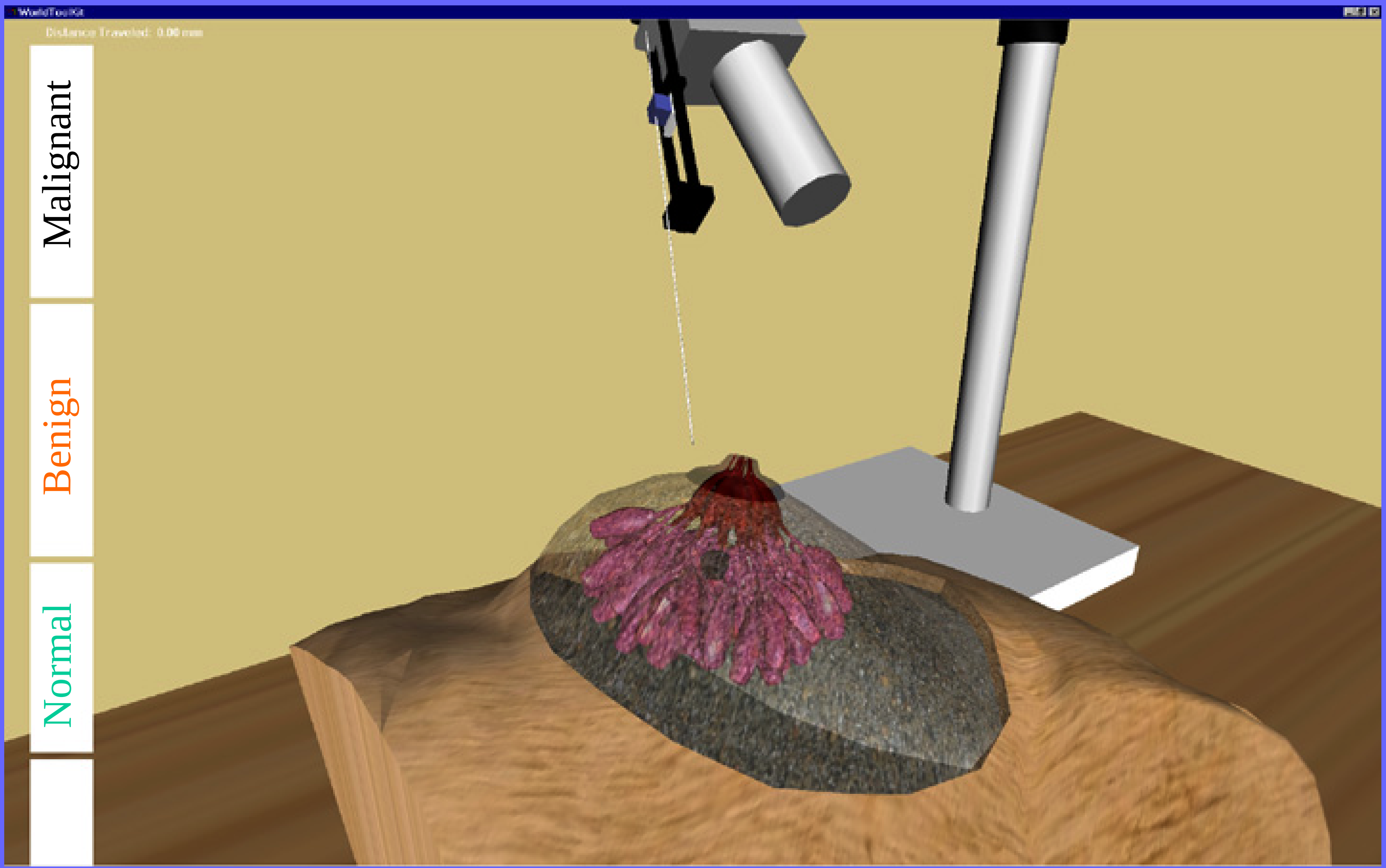
Diana O. Cua, M.D.
Breast Surgeon — Makati Medical Center
Manila, Philippines

Stefanie S. Jeffrey, M.D.
Chief of Breast Surgery
Stanford University School of Medicine

SMART Probe
Image-guided / Multi-modality Sensors

SMART Probe Control
Simple User Interface

SMART Probe Diagnosis
In Vivo, Real-time Interpretation



SMART Software Inputs

Internal / External / Heuristic Information

External Measurements:

- mammograms
- ultrasound scans
- MRI scans
- lymph node sampling
- manual palpitation
- target size/shape
- spiculation
- etc.

Internal Measurements:

- elastic parameters (stiffness)
- optical reflectance
- pO2
- blood flow
- interstitial fluid pressure
- electric parameters
- thermal parameters
- pH
- molecular fingerprint (nanotechnology biosensors)
- etc.

Information Processing

SMART Software

Heuristic information:

- prior medical history
- family medical history
- etc.

Breast Cancer
Diagnostic Parameters

- Mean and median pO_2
  - malignant tumor < normal tissue

- Hypoxic fraction in solid tumors may
  - Influence tumor growth
  - Increase malignant potential
  - Reduce sensitivity to non-surgical treatment modalities

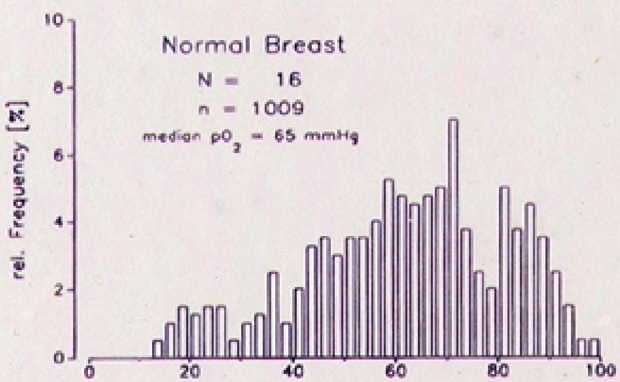
Breast Cancer
Diagnostic Parameters

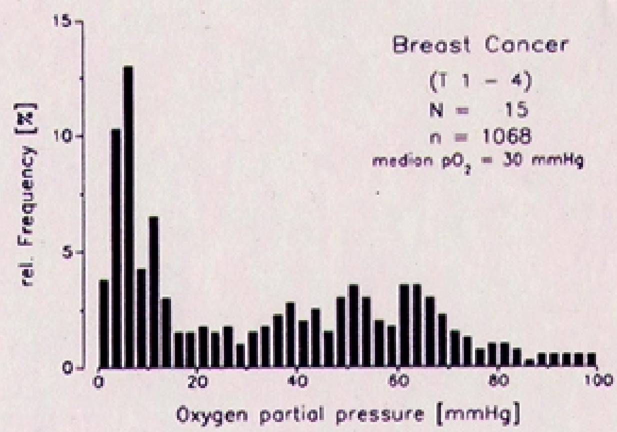
pO_2 as a Breast Cancer Diagnostic Parameter

The mean and median pO_2 values are sig. lower in the malignancies than in the normal tissue

- in normal breast tissue, mean pO_2 is 65 mmHg

- in breast malignancies, mean pO_2 is 28 mmHg



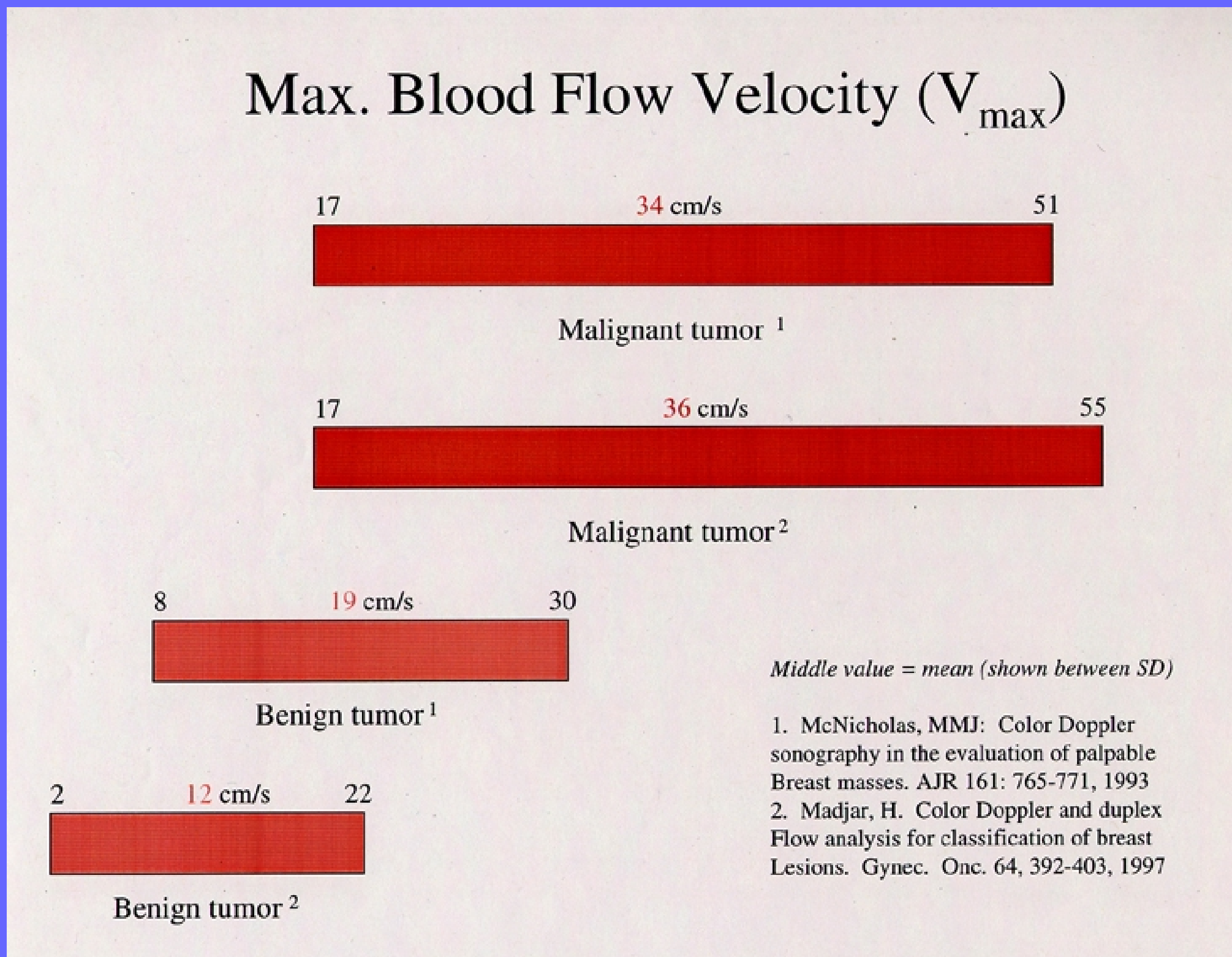


Breast Cancer
Diagnostic Parameters

- Mean blood flow
  - Normal 311 +/- 157 flux
  - Benign 482 +/- 209 flux
  - Malignant 711 +/- 280 flux

Normal < benign < malignant

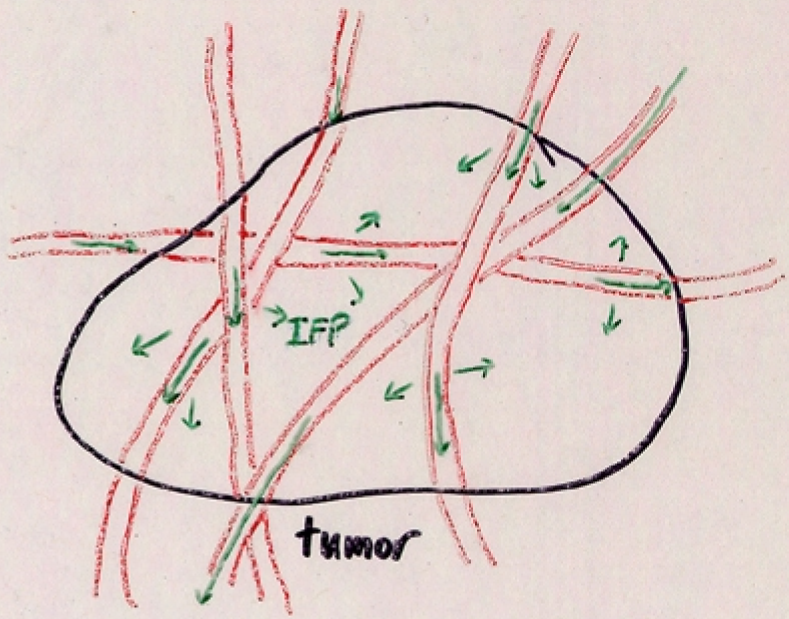
Breast Cancer
Diagnostic Parameters



Breast Cancer
Diagnostic Parameters

IFP as a Breast Cancer Diagnostic Parameter

IFP (Interstitial Fluid Pressure) - the balance of fluid entering a tumor from blood supply and exiting by way of outward fluid flow and vasculature

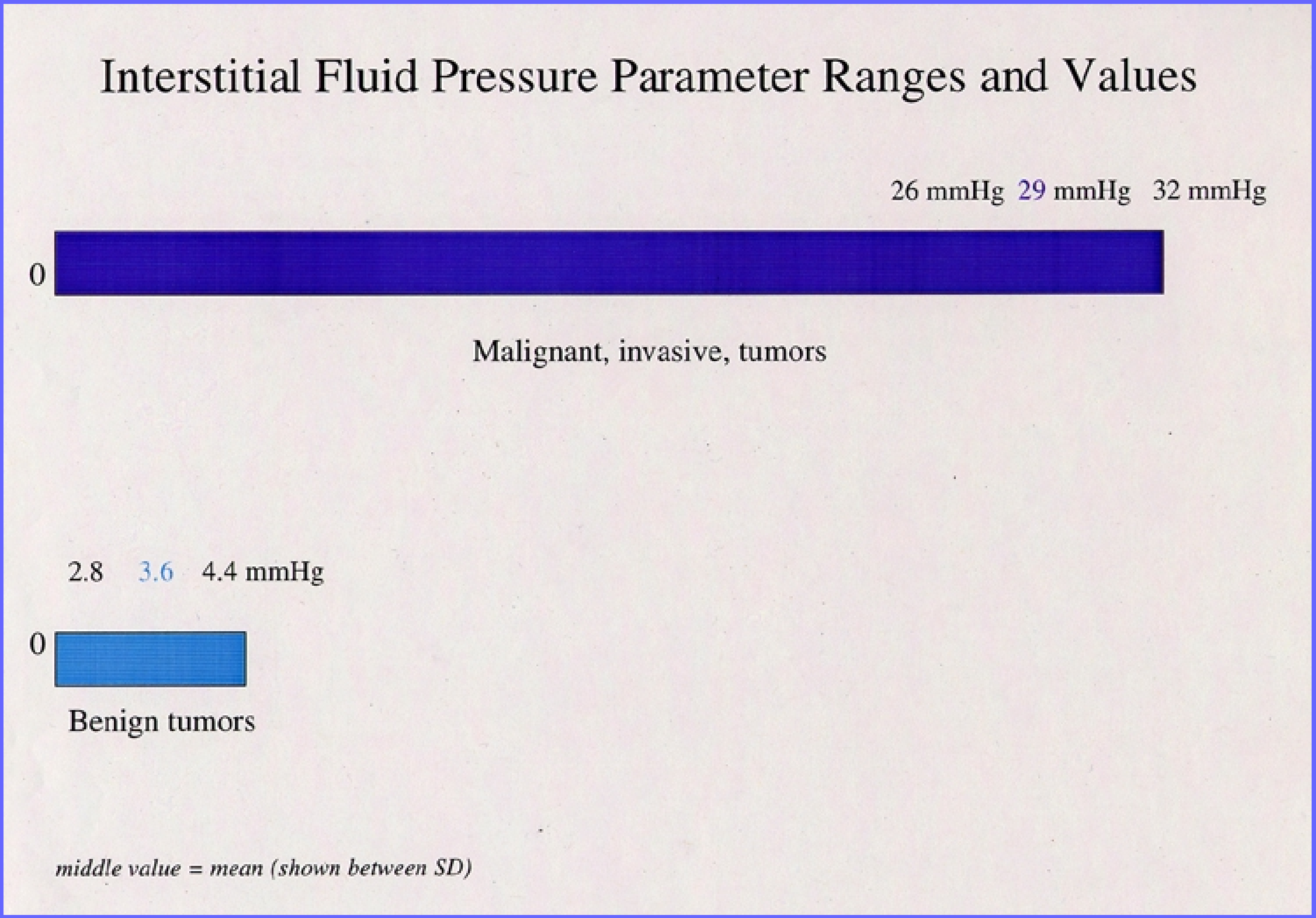


Breast Cancer
Diagnostic Parameters

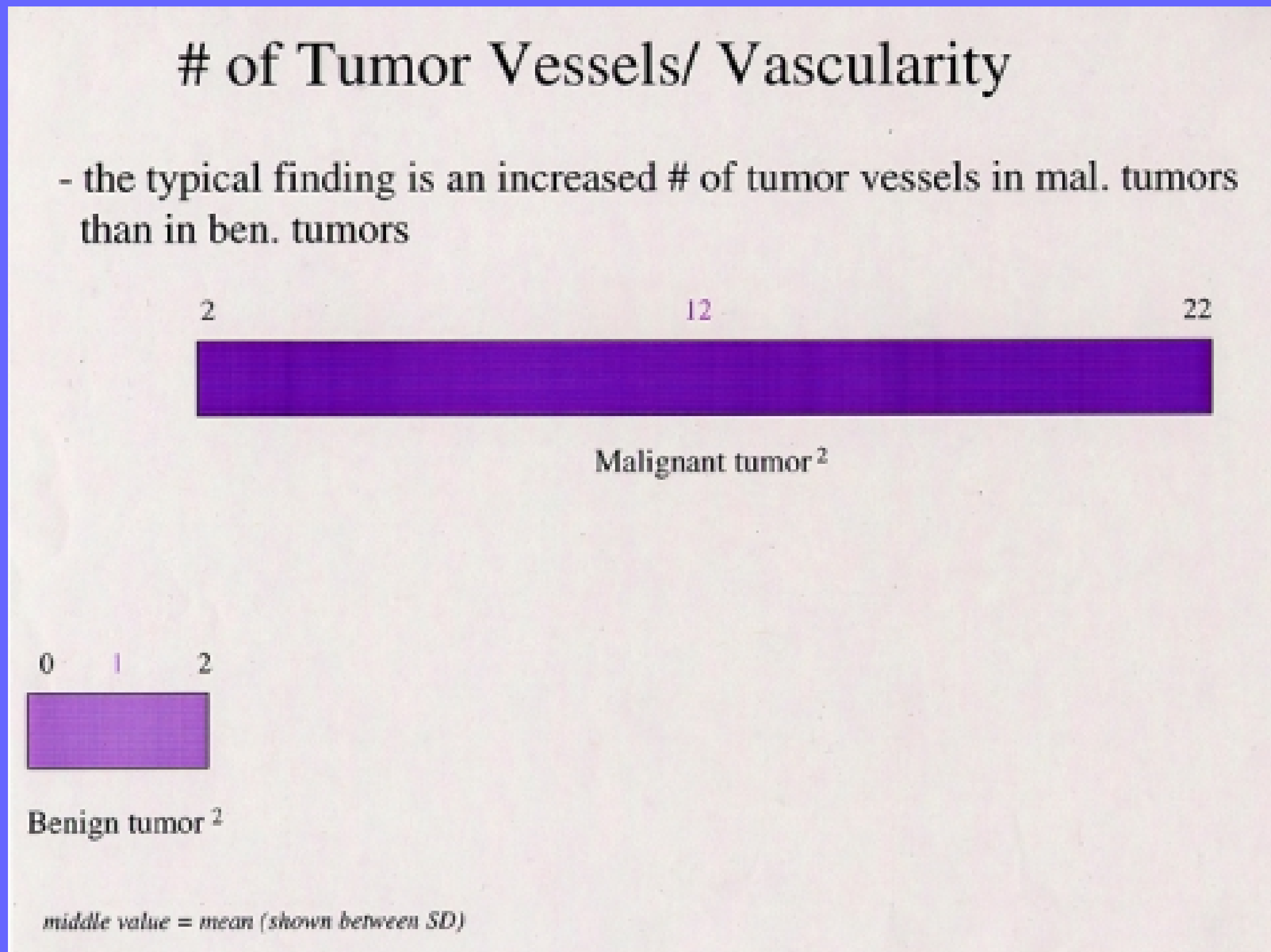
Importance of IFP measurement

- Studies confirm that even the smallest invasive breast cancers exhibit a high IFP wherever the needle tip is located within the tumor.
- Only invasive breast cancer has consistently high IFP.
- Due to the elevated IFP in invasive malignant tumor and significant drop-off values at periphery, IFP readings show great value discrimination between malignant and benign tumors.

Breast Cancer
Diagnostic Parameters



Breast Cancer
Diagnostic Parameters



High microvessel counts represent increased tumor angiogenesis and is correlated with tumor aggressiveness

Breast Cancer
Diagnostic Parameters

pH as a Breast Cancer Diagnostic Parameter

- normal tissue has a pH ranging from 7 - 7.4
- extracellular pH has a lower value (more acidic) than normal tissue

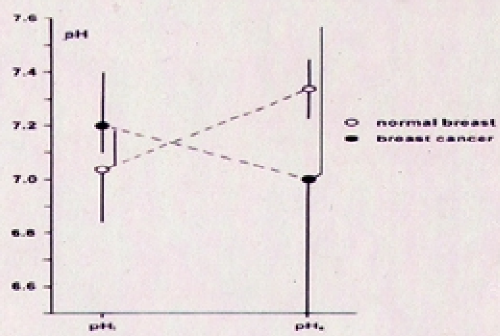
pH_e (normal) - 7.35 $\quad$ pH_e (tumor) - 7.0

- intracellular pH has a higher value (more basic) than normal tissue

pH_i (normal) - 7.04 $\quad$ pH_i (tumor) - 7.2

in tumors, $pH_i > pH_e$

- differences in pH between normal and malignant range from .3 - 1.7



Breast Cancer
Diagnostic Parameters

Elasticity

- Malignant tumors tend to be 10-100x stiffer than normal breast tissue
- Some cancers, such as noninvasive ductal, medullary, and mucinous carcinomas, can be relatively soft

Bioimpedance

- Electrical and dielectric properties measured on normal and cancerous breast tissues:
  - Normal tissues, surrounding tissues, and carcinoma are significantly different (Chauveau; Jossinet & Schmitt)
  - Increased capacitance & resistance in malignant tumors

Breast Cancer
Diagnostic Parameters

External imaging information:

Sonographic Features	Score for Data Inputs: 1 benign tumor	2	3	4	5 malignant tumor
Shape	Very regular	Regular	Intermediate	Irregular	Very irregular
Border	Very smooth	Smooth	Intermediate	Rough	Very rough
Halo	Absent	Mild	Moderate	Marked	Extreme
Internal echoes	Very homogeneous	Homogeneous	Intermediate	Heterogeneous	Very heterogeneous
Posterior echoes	Markedly enhanced	Enhanced	No change	Attenuated	Markedly attenuated
Edge shadows	Extreme	Marked	Moderate	Mild	Absent

Computer-aided tools
- 3D tumor reconstruction (ultrasound sensor attached to robotic arm)
- Feature extraction
- Pattern search / Pattern recognition

Breast Cancer
Prognostic Parameters

- mean pO_2

—metastasizing tumors	7.5 mmHg
—nonmetastasing tumors	20 mmHg
—Disease free survival (70-80%)	>10 mm Hg
—Disease free survival (30-35%)	<10 mm Hg

- Occurrence of hypoxia and O_2 patterns do not correlate with clinical stages
- pO_2 values in malignant tumors are heterogenous throughout hypoxic tissue

Breast Cancer
Prognostic Parameters

¥ MVC (microvessel count)

— MVC has been shown in many studies to be an independent prognostic indicator for relapse free survival

¥ disease-free < 80 vessels/mm < relapse

¥ Microvessel morphology pattern

— none < spotted < linear < mixed patterns < branching

¥ mean malignant tumor size increase in this order

¥ all malignant tumors with spotted or linear proved to be invasive

— branching has highest predictive value for malignant tumor

— lesions with branching pattern in one study — positive predictive value for malignancy of 97%

— no benign lesions demonstrated a predominant branching pattern

SMART Probe Software

Advanced Information Technologies

INPUTS:
Internal / External Measurements
Heuristic Information

Data Mining
Pattern Recognition
Knowledge Discovery

Neural Networks

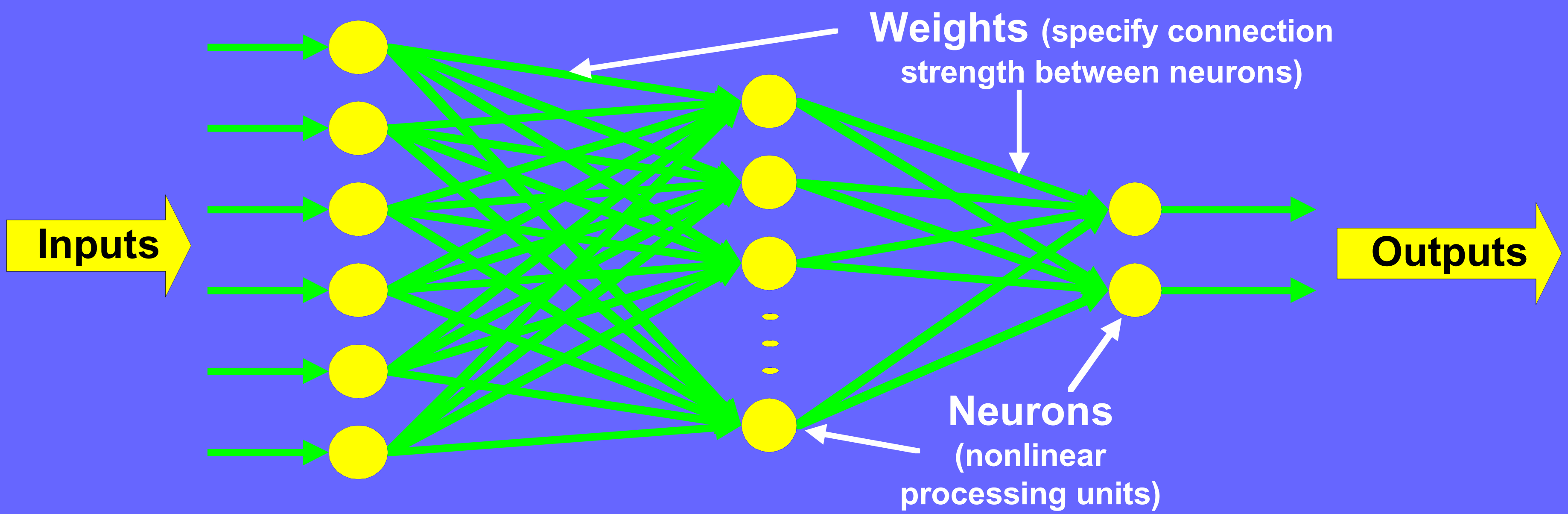
Fuzzy Logic

Information Fusion

OUTPUTS:
Diagnosis / Prognosis

Neural Network Technology

Neural network —signal processing technology inspired by and loosely modeled after the human brain



- Generic nonlinear functional element
- Functionality (defined by weights) set through *training* process
- Several applications in industrial process control, credit scoring, fraud detection, target recognition, optical character recognition, etc.

Fuzzy Logic Technology

Fuzzy logic —signal processing technology inspired by and loosely modeled after human processing of qualitative (fuzzy inference) inputs.

Sonographic Features	Score for Data Inputs 1 benign tumor ◄	2	3	4	5 ► malignant tumor
Shape	Very regular	Regular	Intermediate	Irregular	Very irregular
Border	Very smooth	Smooth	Intermediate	Rough	Very rough
Halo	Absent	Mild	Moderate	Marked	Extreme
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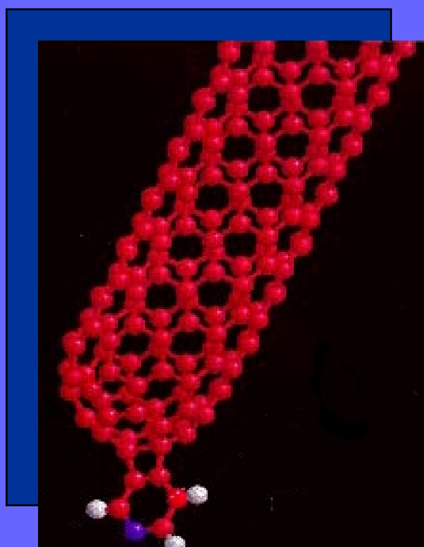
Posterior echoes	Markedly enhanced	Enhanced	No change	Attenuated	Markedly attenuated
Edge shadows	Extreme	Marked	Moderate	Mild	Absent

¥ Functionality set through *correlation* process

¥ Several applications in industrial process control, credit scoring, fraud detection, target recognition, optical character recognition, etc.

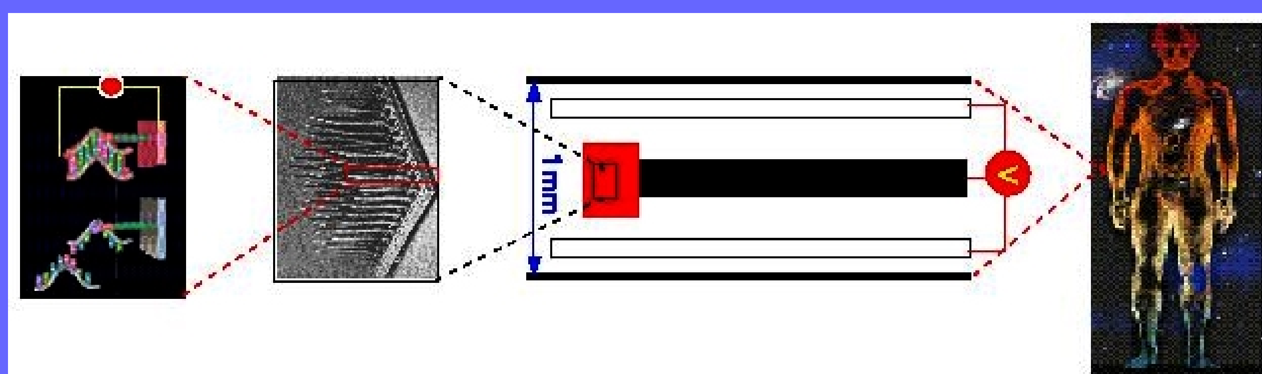
Nanotechnology

Micro/Nanoscale Biosensors

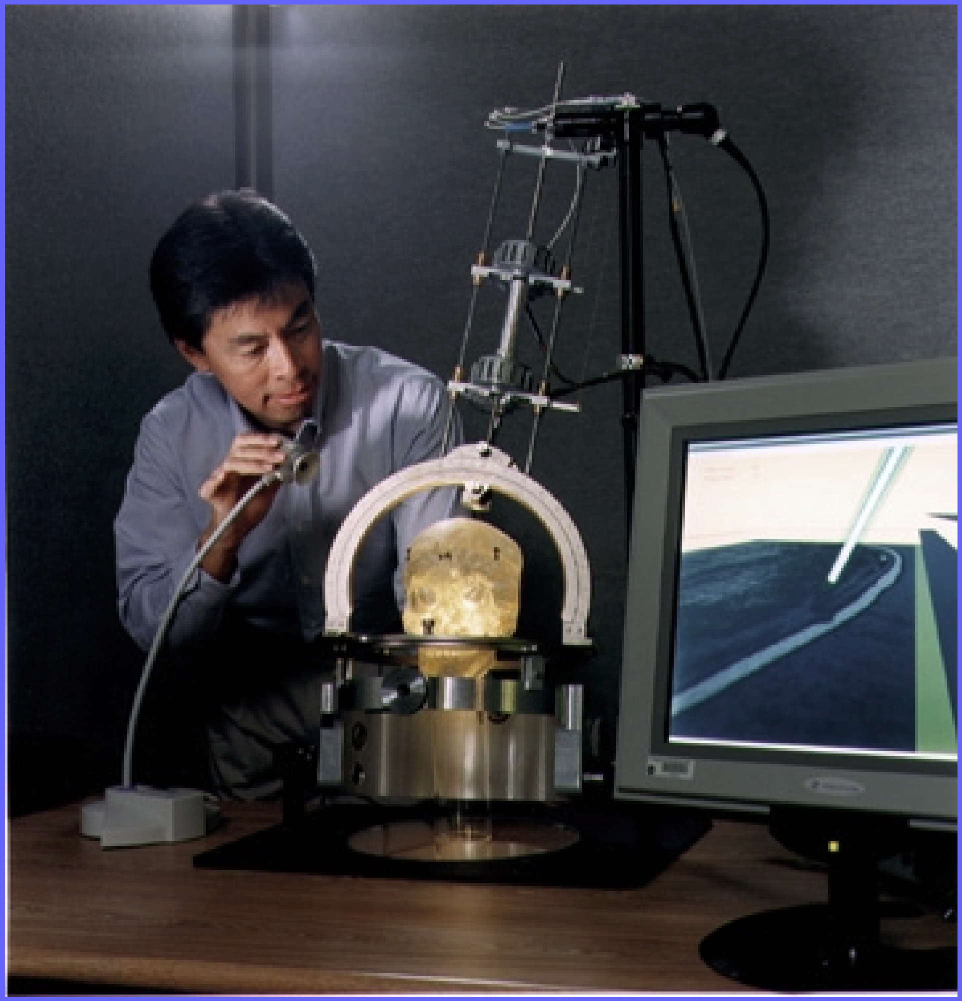


Detection of Biomolecular Signatures:

- Developing biosensors to study origins of life
- Collaborating with National Cancer Institute (NCI) to develop sensors for cancer diagnosis



SUMMARY
Other Medical Applications



Neurosurgery SMART Probe

SMART Probe
Benefits

- ¥ Real-time tissue diagnosis
- ¥ Avoid injury to arteries, nerves, etc.
- ¥ Determine tumor margins
- ¥ Accurate localization of tumor
- ¥ Accurate treatment & monitoring
- ¥ etc.

SMART Probe
Breast Cancer Diagnosis

- Information Technologies to assist astronauts in responding to medical emergencies during space missions will be employed to improve medical care in the form of smart medical tools.

- This technology has great potential for the diagnosis & treatment of cancer.

- Joint research project between NASA & Stanford Medical Center - to develop a smart probe to identify & diagnose whether a suspicious breast tissue is benign or malignant.

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Information Sciences & Technology
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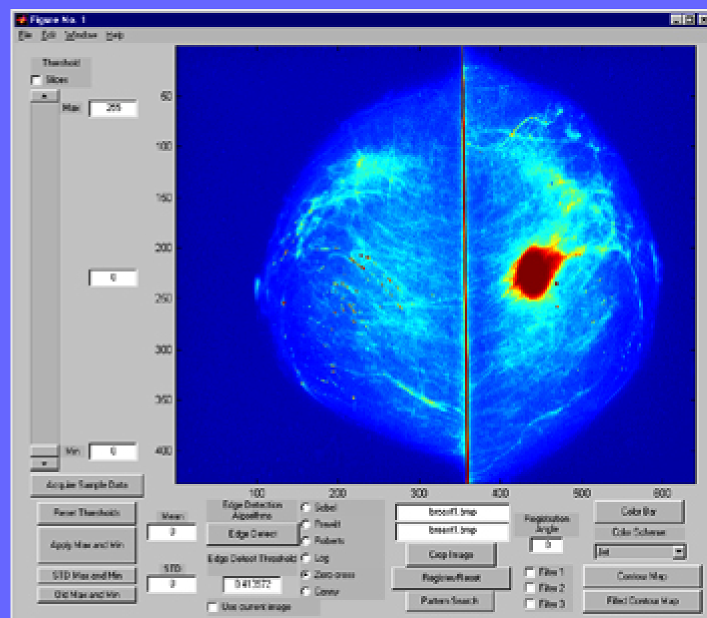
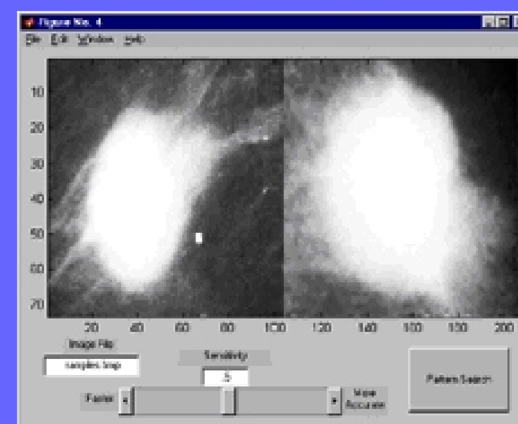
SMART Probe
Computer-aided Tools

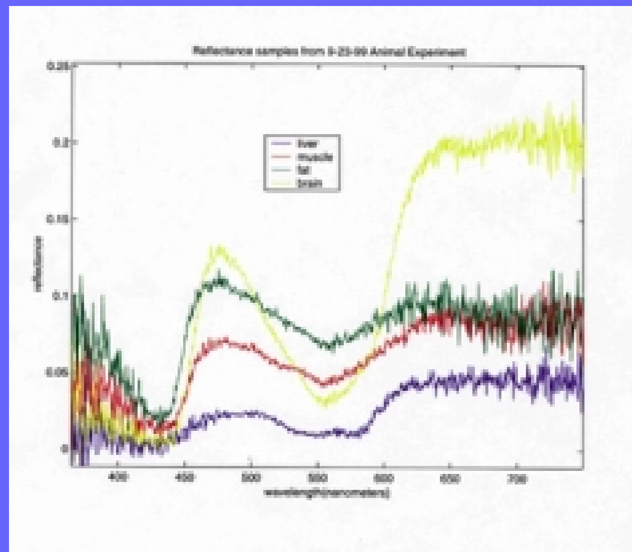




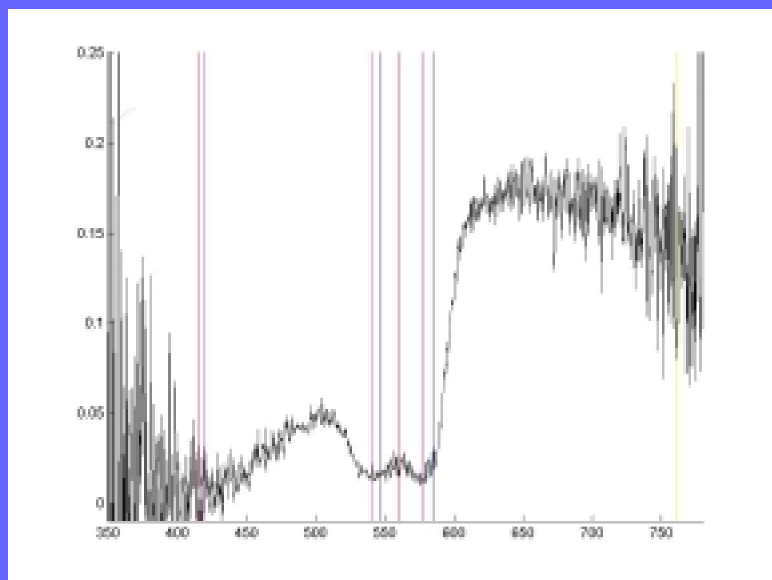
- Image enhancement
- Pattern search / Pattern recognition
- 3D tumor reconstruction
- Feature extraction

SMART Probe

Data Sample (optical reflectance)

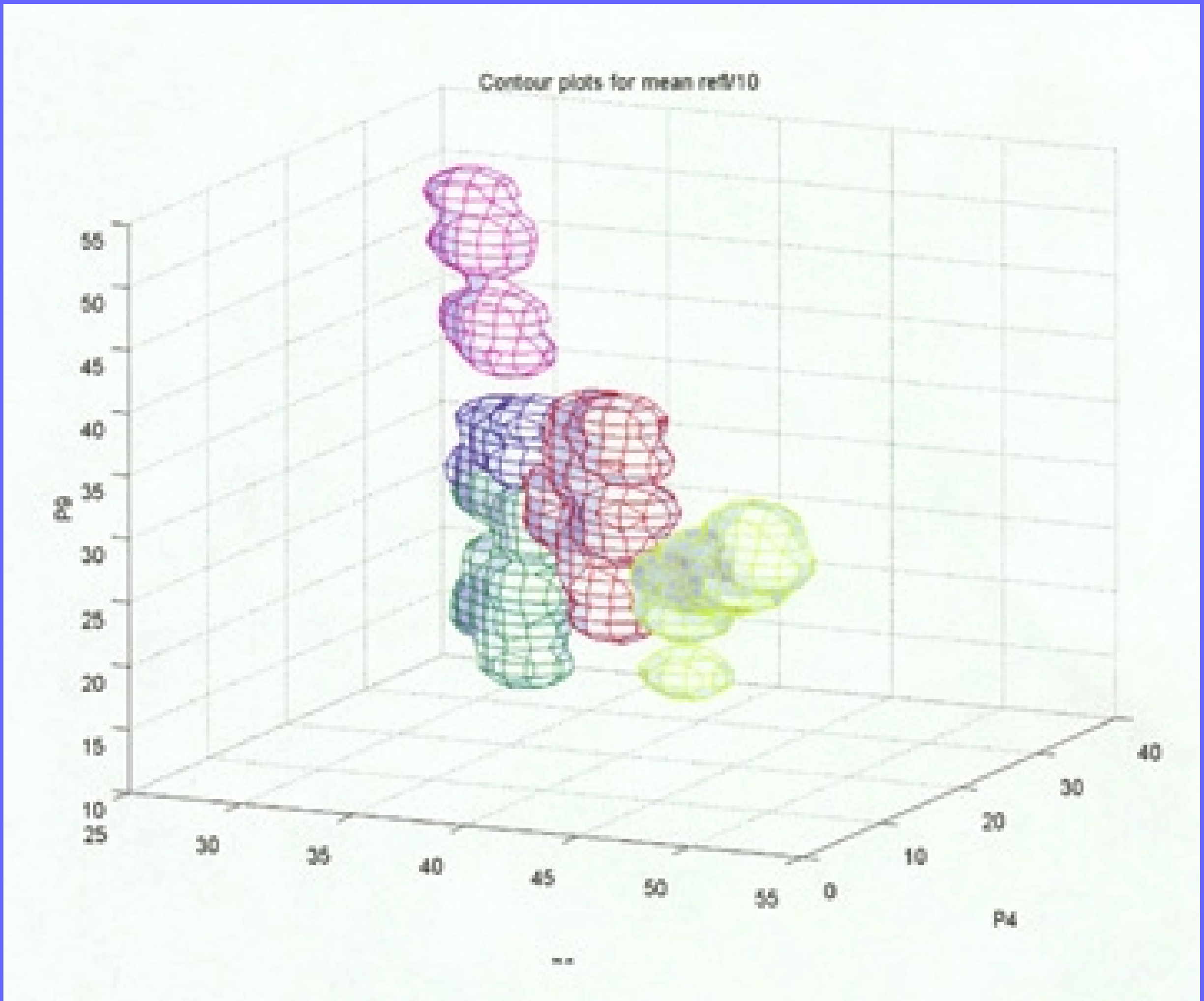


Normal tissues



Mammary tumor (MCF – 7)

SMART Probe
Characterizing Tissue Types



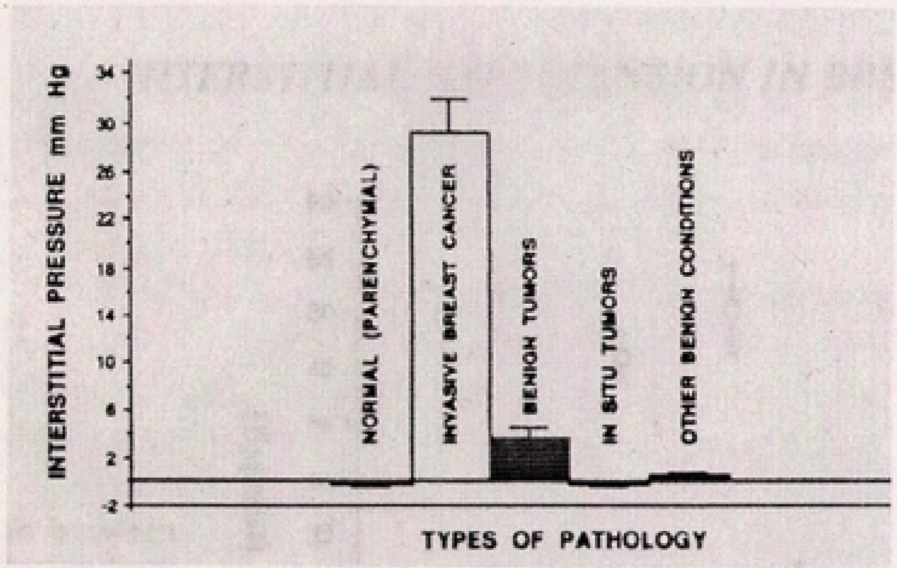
Parameter Clustering in High Dimensional Space

Final Remark
Commercial Version

Silicon Valley start up company is developing a commercial version of NASA s Breast Cancer SMART Probe

Breast Cancer
Diagnostic Parameters

IFP Parameter Ranges and Values (cont.)



* Nathanson SD, Nelson L. Interstitial Fluid Pressure in Breast Cancer, Benign Breast Conditions, and Breast Parenchyma. *Annal Surg. Oncol.* 1994; 1(4): 333-338

Breast Cancer
Diagnostic Parameters